REMARKS

Reconsideration is respectfully requested. Claims 13-24, 26-32, and 34 have been amended. Claim 33 is reiterated. Claims 1-12 were previously cancelled. Claims 13-34 are pending.

The amendments herein to above-mentioned claims only clarify the subject matter of the present invention and are not made for purposes of patentability. No subject matter has been disclaimed, and the amendment of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. No new matter has been added. Applicants expressly reserve the right to pursue identical or similar claims in other patent applications that are identical or similar to the claims amended or canceled in this response.

Claim 13, as amended, is directed to a **compound** comprising a **therapeutic agent** covalently connected to a **chemically reactive entity** by means of a **cleavable linking entity**, is fully supported by the specification as originally filed. Amended claim 26, which recites a composition including a **compound** which comprises **a therapeutic agent** covalently connected to a **chemically reactive entity** by means of a **cleavable linking entity**, is also fully supported by the specification as originally filed.

At page 3, lines 18 to 20, the specification relates to "a first compound comprising a chemically reactive entity which is capable of forming covalent bonds with functionalities present on proteins, joined by a covalent bond or a first linking group to an agent of interest." The specification thus provides support for the term "**chemically reactive entity**." The terms "linking group" and "linking entity" are used interchangeably. The term "linking group" (page 3, line 20) together with the explanations given in the paragraph bridging pages 5 and 6 thus provide support for the term "**linking entity**." At page 12, lines 15 -18, the specification provides support for "**cleavable linking entity**." Support for the term "**therapeutic agent**" as an agent of interest may be found at page 3, lines 15-16 and lines 18-25.

Dependent claims 14-25 and 34 have been amended in view of the amendment to claim 13. Claim 17 has also been amended to correct a clerical error.

Claims 27-32 have been amended in view of the amendment to claim 26.

Claim Rejections – 35 U.S.C. § 112, first Paragraph

The Examiner has rejected claims 13-34 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. In particular, the Examiner alleges that there is no support in the specification for the expression "a therapeutic compound of the formula X-Y-Z." The Examiner also alleges that the word "antiproliferative" is only mentioned in passing and that the expression "antiproliferative agents" is only mentioned as a general proposition on page 16.

Without admitting or acquiescing to the Examiner's rejection, the claims no longer recite the "formula X-Y-Z." With respect to this claim term, this ground for rejection is now moot.

The specification provides extensive written description support for the amended claims. As noted, at page 3, lines 18 to 20, the specification relates to "a first compound comprising a chemically reactive entity which is capable of forming covalent bonds with functionalities present on proteins, joined by a covalent bond or a first linking group to an agent of interest." The specification thus provides support for the term "**chemically reactive entity**." The term "linking group" (page 3, line 20) together with the explanations given in the paragraph bridging pages 5 and 6 thus provide explicit support for the term "**linking entity**," the terms being interchangeable. At page 12, lines 15 -18, the specification provides support for "**cleavable linking entity**." Support for the term "**therapeutic agent**" as an agent of interest may be found at page 3, lines 15-16 and lines 18-25.

One of skill in the art would readily understand that an "**antiproliferative drug**," which is fully supported at page 16, line 14, and disclosed as being an agent or compound of interest, can be incorporated into the claimed compounds. The expression "agent of interest" (page 3, line 20), together with the explanations given in the paragraph bridging pages 15 and 16, and on page 16, lines 4 to 11, and lines 12 to 15, provide explicit support for the term "**antiproliferative drug**" of

amended claim 34. In the paragraph bridging pages 15 and 16 examples of agents of interest are given, and on page 16, lines 4 to 11, "other compounds of interest" are disclosed. Among potential compounds or agents of interest, agents or compounds of particular interest are specified on page 16, lines 12 to 15. More particularly, on page 16, line 14 "**antiproliferative drugs**" are disclosed.

In view of the above, claims 13-34 satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Applicants respectfully request that this rejection be withdrawn.

Priority Claims to Parent Applications

With respect to the priority claim to U.S. patent application 07/592,214 filed on October 3, 1990, the present application, as originally filed, is a continuation of U.S. patent application 08/237,346 filed on May 3, 1994, and has an identical specification. For the reasons articulated above, the claimed subject matter is fully supported by the specification. The present application therefore has a priority date of at least May 3, 1994.

Claim Rejections 35 U.S.C § 102(a)

Claims 13, 23, 26, 30 and 34 have been rejected under 35 U.S.C. §102(a) as being anticipated by Kratz et al.

Kratz et al. was published after the May 3, 1994 filing date of parent application 08/237,346. Kratz et al. is therefore not prior art under 35 U.S.C § 102(a).

Applicants respectfully request that this ground for rejection be withdrawn.

Claim Rejections 35 U.S.C § 103(a)

Claims 13, 23, 26, 30 and 34 have been rejected under 35 U.S.C. §103(a) as being obvious over Someno et al. (Published abstract of JP 0107820).

The Cited Reference

The cited reference discloses peplomycin-polylysine-maleimide complexes which can be bound to cytotoxic substances, imaging components, and monoclonal antibodies. The Examiner

alleges that the peplomycin is the therapeutic agent (specifically an antiproliferative drug), polylysine is a linking entity, and maleimide as a chemically reactive group.

The Cited Reference Distinguished

The Examiner fails to satisfy the requirements to establish a prima facie case on multiple grounds. Specifically, 1) the references does not teach or suggest all claim limitations; 2) the cited reference combined with the general knowledge in the art does not include a suggestion or incentive to modify the reference; and 3) the modifications does not have a reasonable chance of success.

First, the reference fails to disclose multiple elements of the pending claims.

The reference fails to teach that maleimide, as the "chemically reactive functionality" of the cited reference, reacts *in vivo* with a reactive functionality on an endogenous vascular or blood component protein to form a covalent bond therewith, as required by the claims. The reference fails to teach covalent bonding to any blood component or protein. Instead, the reference discloses only that free NH_2 groups of the present compounds can be bound by monoclonal antibodies, and that the resulting complex can be used to study cell selectivity. With respect to antibody binding, the free NH_2 groups of the peplomycin-polylysine-maleimide are found on the polylysine linking group, not the maleimide "chemically reactive functionality" cited by the claims. Moreover, antibody binding is non-covalent. With respect to binding to cells, the reference does not teach that the cells include endogenous vascular or blood component protein, or that the complex forms a covalent bond with the cells. Further, the reference otherwise fails to disclose, mention, or hint at "a reactive functionality on an endogenous vascular or blood component protein," as required by the claims.

In addition, the reference fails to teach that the chemically reactive entity forms a covalent bond with a reactive functionality selected from the group consisting of an amino, carboxylate, or thiol reactive functionality, as required by the claims. The reference fails to disclose, mention, or hint at any of these functionalities. The reference therefore fails to meet this limitation of the rejected claims.

The reference also fails to teach that the linking entity, polylysine, is an *in vivo* cleavable linking entity. The cited reference makes no mention that polylysine as a linking entity that is cleavable, or cleavable *in vivo*. Moreover, the Examiner fails to provide any additional reference or

support for the proposition that polylysine is cleavable *in vivo*. In the absence of any such support, the cited reference fails to meet this limitation.

Second, the Examiner fails to provide the requisite motivation to alter the teachings of the references. The reference fails to provide any motivation or suggestion for one of skill in the art to form a covalent bond between maleimide and a reactive functionality of an endogenous vascular or blood component protein. The reference fails to provide any motivation or suggestion for one of skill in the art to form a covalent bond between the maleimide "chemically reactive group" and a reactive functionality selected from the group consisting of an amino, carboxylate, or thiol reactive functionality. Finally, the reference provides no motivation or suggestion to cleave a polylysine linking entity *in vivo*. The Examiner provides no other motivation or suggestion for these modifications.

Third, the reference and the Examiner fail to provide a reasonable expectation for success in modifying the teachings of the cited reference. The cited reference provides no teaching that would provide one of ordinary skill with a reasonable expectation of bonding maleimide to a reactive functionality of an endogenous vascular or blood component protein, forming a covalent bond between maleimide and a reactive functionality selected from the group consisting of an amino, carboxylate, or thiol, or cleaving polylysine *in vivo*. The Examiner provides no other reference or teaching that would provide a reasonable expectation of success in modifying the compound in the cited reference.

In view of the above, amended claims 13, 23, 26, 30 and 34 are not obvious over Someno et al. under 35 U.S.C § 103(a). Applicants respectfully request that this ground for rejection be withdrawn.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal form is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **500862000105**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By _____

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